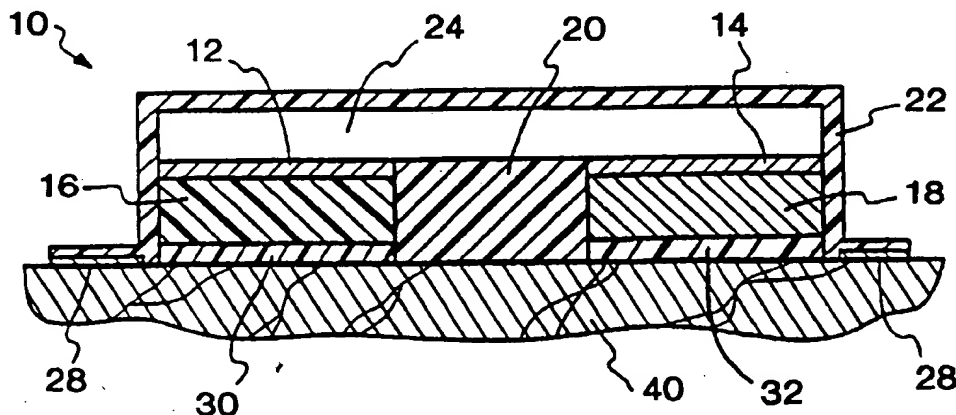


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61N 1/30, 1/32		A1	(11) International Publication Number: WO 98/28038
			(43) International Publication Date: 2 July 1998 (02.07.98)
(21) International Application Number: PCT/US97/23345 (22) International Filing Date: 17 December 1997 (17.12.97) (30) Priority Data: 60/034,065 24 December 1996 (24.12.96) US (71) Applicant (for all designated States except US): ALZA CORPORATION [US/US]; 950 Page Mill Road, Palo Alto, CA 94303-0802 (US). (71) Applicant (for US only): ECKENHOFF, Bonnie, J. (executrix for the deceased inventor) [US/US]; 1080 Autumn Lane, Los Altos, CA 94024 (US). (72) Inventor: ECKENHOFF, James, B. (deceased). (74) Agents: ROGERS, Christopher, P. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: METHOD AND DEVICE FOR CONTROLLING MAMMALIAN REPRODUCTIVE CYCLE**(57) Abstract**

A method encompasses the substantially continuously electrotransport delivery of luteinizing hormone releasing hormone (LHRH), prologues, analogues, salts or mixtures thereof, preferably at a substantially constant rate, to a female mammal for the purpose of modifying its reproductive cycle. An electrotransport device substantially is suited for the continuous delivery of LHRH prologues, analogues, salts or mixtures thereof over an extended period of time to a mammal. The present technology may be successfully applied to the controlled breeding of mammals, such as thoroughbred race horses.

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1 **METHOD AND DEVICE FOR CONTROLLING**
2 **MAMMALIAN REPRODUCTIVE CYCLE**

3
4
5 TECHNICAL FIELD

6
7 This invention relates to the controlled delivery of leutinizing hormone
8 releasing hormone (LHRH) or an analog of LHRH by electrotransport to
9 female animals, particularly female breeding animals, to control ovulation.
10 More particularly, this invention relates to the transdermal electrotransport
11 delivery of LHRH or an analog thereof to mares to control the time of birth of
12 a colt.

13
14 BACKGROUND ART

15
16 The ability to control an animal's date of birth is generally of importance
17 in animal breeding. More particularly, the economic considerations
18 surrounding the breeding of some species, e.g., thoroughbred race horses,
19 have traditionally inspired creative scientific approaches to equine breeding.
20 The ability to accurately and precisely select equine birth dates is especially
21 important in light of the official determination, by the breeder's association, of
22 January 1 as the universal birth date of thoroughbred horses for racing
23 purposes. That is, all horses born within a calendar year are presumed to
24 have a January 1 birth date for racing purposes. Thus, animals born earlier
25 within any given calendar year have a significant developmental advantage
26 over those born later in the same year. Accordingly, substantial research and
27 development efforts have been directed at controlling the equine reproductive
28 cycle in order to produce horses with actual birth dates on or shortly after
29 January 1 and, thereby, augment the developmental state of thoroughbred
30 horses.

1 Female horses experience estrous cycles about 21-23 days in length,
2 with some seasonal variations, except for a period of about two to five
3 months. During the latter period, the mare typically experiences an anestrus
4 period, i.e. a period of sexual inactivity. This period commonly ranges in the
5 northern hemisphere from about November to March (see, for example, The
6 Horse, J. W. Evans, 2nd Ed., pp. 351- 373, W.H. Freeman & Co. (1990)).
7 However, since the gestation period of the mare is about 335-340 days,
8 February is the ideal month for mare impregnation in order to achieve an
9 early birth date in the following calendar year, i.e. in January or February.
10 Since in the northern hemisphere mares typically go through their yearly
11 anestrus period during these months, the onset of estrus to attain an early
12 birth date must be induced artificially.

13
14 In the northern hemisphere, the largest number of mares experience
15 ovulation during the longest daylight periods of June. The observation of this
16 correlation between extended daylight periods and increased mare ovulation
17 rates led to the management of equine breeding by "extending the
18 photoperiod". Thus, ovulation has been induced during the anestrus period
19 by placing mares under artificial lighting to, thereby, extend the perceived
20 daylight period up to about 16 hours per day.

21
22 Both follicular development and the onset of ovulation are dependent
23 on the presence of certain hormones, such as luteinizing hormone (LH),
24 follicle-stimulating hormone (FSH), estrogen, and progesterone (see, for
25 example, D. Freeman et al., "Mare management", Large Animal Vet.: 6-8
26 (July/Aug., 1992)). The blood levels of these hormones vary in a relatively
27 predictable manner during the normal female equine reproductive cycle.
28 Ovulation has also been induced in a mare by delivery of pharmaceuticals
29 which interfere with the hormonal cycle of the mare. Prostaglandin and its
30 analogues, for example, have been delivered to mares to cause the
31 regression of the corpus luteum, and to thereby attain a reduction of the

1 estrous period. Progesterone has also been delivered to either suppress or
2 synchronize the heat periods in mares having long and erratic estrous cycles.

3
4 LHRH (also known as gonadotropin releasing hormone or GnRH) and
5 follicle-stimulating hormone (FSH) have been employed to alter the female
6 equine reproductive cycle. LHRH has been delivered to equines by various
7 methods, including injection and implantation. For instance, LHRH has been
8 delivered by intravenous and intramuscular injection in order to determine its
9 effect on the release of luteinizing hormone (LH) and ovulation (see, J.E.
10 Turner, "The Effect of Various Gonadotropin-releasing Hormone Regimes on
11 Gonadotrophins, Follicular Growth and Ovulation in Deeply Anoestrous
12 Mares", J. Reprod. Fert. Suppl. 44:213-225 (1991)). LHRH has also been
13 successfully delivered to mares from subcutaneously implanted osmotic
14 minipumps, which are commercially available from ALZA Corporation, Palo
15 Alto, California) to induce ovulation (see, C.G.V., Ainsworth, "Continuous
16 Infusion of Gonadotropin-releasing Hormone (GnRH) Advances the Onset of
17 Oestrous Cycles in Thoroughbred Mares on Australian Stud Farms", J.
18 Reprod. Fert., Suppl 44:235-240 (1991)).

19
20 Although some induction of ovulation was attained in mares by
21 injection and implantation of LHRH and its analogs, there are drawbacks
22 associated with these delivery techniques. One important problem associated
23 with injections is the pulsatile nature of the delivery, which typically cannot
24 provide the desired uniformity of drug concentration in the bloodstream.
25 Another problem with injecting LHRH is its short half life, requiring frequent
26 injections to maintain LHRH plasma levels. Another problem associated with
27 this, and other non-continuous delivery systems, is that they require repeated
28 human intervention by highly trained personnel to administer injections on a
29 regular basis. On the other hand, implantation techniques have unique
30 problems associated with the surgical procedure required for the
31 subcutaneous insertion of the device. These problems require sterilization to

1 prevent infections, which increase labor costs, and produce significant mare
2 discomfort, which may cause rubbing or scratching at the implantation site.

3
4 As used herein, the term "electrotransport", refers generally to the
5 passage of a substance through a body surface, such as skin, mucous
6 membrane, or nails, induced at least partially by an electrical field. For
7 example, a therapeutic agent may be introduced into an animal's body by one
8 of several electrotransport processes. One form of electrotransport, called
9 iontophoresis, involves the electrically induced transport of charged ions.
10 Another type of electrotransport, electroosmosis, involves the movement of a
11 liquid and all agents, including uncharged agents, dissolved therein under the
12 influence of an electric field. Still another type of electrotransport,
13 electroporation, involves the transport of an agent through transiently-existing
14 pores formed in the skin or other biological membranes by the application of
15 an electric field. In any given electrotransport process, however, more than
16 one of these processes may be occurring simultaneously to some extent.
17 Accordingly, the term "electrotransport" is used herein in its broadest possible
18 meaning, which includes the electrically induced or enhanced transport of at
19 least one agent, which may be charged, or uncharged, or mixtures thereof,
20 regardless of the specific mechanism or mechanisms by which the agent is
21 actually transported.

22
23 Sibalis U.S. Patents 5,013,293; 5,312,325 and 5,372,579 all disclose
24 an electrolytic transdermal patch provided with a current oscillator for the
25 periodic delivery of LHRH to induce or inhibit ovulation. The patent teaches
26 delivering "pulses" of electrotransport current, each pulse being about 6
27 minutes in duration, at a frequency of one 6 minute pulse per hour, to deliver
28 LHRH to women in order to match the body's natural release of LHRH and
29 thereby induce ovulation. However, the delivery of LHRH at a frequency of
30 two or more 6 minute pulses per hour is said to completely extinguish

1 gonadotrophic secretion and inhibit ovulation (see, column 2, lines 44-57 and
2 column 6, lines 16-30 of Sibal U.S. 5,013,293).

3

4 There is still a need for an effective method of non-invasively delivering
5 LHRH, or an analog thereof, to successfully attain scheduled ovulation,
6 insemination and/or pregnancy, particularly for breeding animals (eg, cattle
7 and horses) and more particularly for breeding animals having seasonal
8 anestrus periods.

9

10 DESCRIPTION OF THE INVENTION

11

12 This invention provides a method of controlling the estrous cycle,
13 inducing ovulation during an anestrus period, and/or restarting the estrous
14 cycle of a female mammal which is already experiencing some stage of the
15 estrous cycle. This is attained by non-invasively and continuously delivering
16 LHRH, or an analog thereof, to female mammals by transdermal
17 electrotransport. In one embodiment of the invention, a substantially constant
18 electrical potential is applied to deliver the LHRH across a body surface of the
19 mammal. This electrical potential induces or enhances the transport of the
20 LHRH through the body surface, preferably in a substantially continuous
21 manner, and more preferably at a substantially constant rate.

22

23 The present invention can be used in the breeding of animals such as
24 cattle and horses. For example, the invention may be used to ensure that
25 one or more female breeding animals (eg, an entire herd) are ovulating at the
26 same time so that the animals can be inseminated (ie, by artificial
27 insemination) at the same time, thereby making the use of insemination
28 materials and the scheduling of veterinary visits more efficient. The invention
29 has particular utility in controlling the ovulation of female thoroughbred race
30 horses. In one preferred embodiment, the hormone is continuously delivered
31 by transdermal electrotransport to a female equine (mare) to induce ovulation

1 at a time when the mare is normally in a seasonal anestrous period, after
2 which the mare is naturally or artificially inseminated to achieve impregnation
3 at a seasonal time which results in the colt being born soon after January 1.
4 In another preferred embodiment, the hormone is continuously delivered by
5 transdermal electrotransport to female breeding animals (eg, cattle, sheep,
6 pigs, etc) to induce ovulation at a time when the animal is normally in a
7 seasonal anestrous period, after which the animals (eg, an entire head) are
8 artificially inseminated to achieve impregnation.

9

10 BRIEF DESCRIPTION OF THE DRAWINGS

11

12 Fig. 1 is a sectional view of one embodiment of a transdermal
13 electrotransport device useful in accordance with the present invention.

14

15 Fig. 2 is a graph showing typical concentrations of selected hormones
16 in the blood serum of a horse as a function of time during the horse's estrous
17 cycle.

18

19 Fig. 3 is a graph showing blood progesterone and leuteinizing hormone
20 (LH) levels in a mare participating in a clinical study described in Example 1.

21

22 Fig. 4 is a graph showing blood progesterone and leuteinizing hormone
23 (LH) levels in another mare participating in the clinical study described in
24 Example 1.

25

26 Fig. 5 is a graph showing blood progesterone and leuteinizing hormone
27 (LH) levels in yet another mare participating in the clinical study described in
28 Example 1.

29

30 Fig. 6 is a cross sectional view of the electrotransport delivery device
31 used in the in vivo studies of Example 2 herein.

1
2 MODES FOR CARRYING OUT THE INVENTION
3

4 The term "LHRH", as used herein, includes all the natural and synthetic
5 analogs and prodrugs (eg, esters) of LHRH, including LHRH and salts of
6 LHRH, such as, gonadorelin acetate, eg. LUTREPULSE (sold by Ortho
7 Pharmaceuticals, Raritan, N.J.); Cystorelin (sold by Abbott Laboratories, N.
8 Chicago, IL); Hypocrine (sold by Tanabe Seiyaku Co., Ltd., Osaka, Japan);
9 Lutrelef (sold by Ferring AB, Malmo, Sweden); LHRH acetate (eg, Ovarelin);
10 LHRH hydrochloride (e.g. Factrel, sold by Wyeth-Ayerst, New York, NY);
11 Goserelin and its salts (eg, Zoladex, sold by Zeneca Pharmaceuticals,
12 London, UK); Leuprolide and its salts (eg, Carcinil and Lucrin, both sold by
13 Abbott Laboratories); Lupron (sold by TAB, N. Chicago, IL; gonadotropin-
14 releasing factor; gonadotropin-releasing hormone (GnRH); prodrugs thereof,
15 analogs thereof, salts thereof, and mixtures thereof, among others. Of
16 these, water soluble salts of LHRH and analogs of LHRH are most preferred.

17
18 The present invention provides for the non-invasive electrotransport
19 delivery through a body surface (eg, skin of an animal) of LHRH in a
20 substantially continuous manner in order to induce ovulation. The LHRH is
21 preferably delivered in a substantially continuous manner, and more
22 preferably at a substantially continuous rate, over a period of time effective to
23 induce ovulation.

24
25 This invention, therefore, generally relates to a method of modulating
26 the reproductive cycle of a female mammal by electrotransport administration,
27 through a body surface of the mammal, of a composition comprising LHRH, in
28 a substantially continuous manner, preferably, at a substantially constant rate.
29 In one preferred embodiment, the LHRH is administered over a period of time
30 effective to induce ovulation. The continuous administration of LHRH to a
31 mammal in an estrous cycle over a predetermined number of days restarts

1 ovulation without inhibiting the estrous cycle, as occurred with the pulsatile
2 method of the prior art.

3
4 The LHRH is preferably continuously delivered by electrotransport for
5 at least about 80%, preferably for at least about 90%, and more preferably for
6 at least about 95% of the administration period. In some cases, the LHRH
7 may be administered for about 98 to 99%, and even up to about 100% of the
8 administration period. The electrotransport delivery of LHRH generally
9 produces increased secretion of luteinizing hormone (LH) and a
10 corresponding increase in serum LH concentration within about 5 to 10 days
11 after starting the administration. The administration of the LHRH may be
12 commenced during an estrous period to restart the estrous cycle at a
13 predetermined time, generally about 3 to 7 days after commencement of
14 delivery. The administration of the agent may also be started within an
15 anestrous cycle to start the estrous cycle at a predetermined time, generally
16 about 3 to 7 days thereafter. The rate of LHRH delivery remains, preferably,
17 substantially constant over the administration period. This means that the
18 amount of LHRH delivered through the body surface in any given unit of time,
19 e.g., 1 hour, remains within about 30%, more preferably within about 20%,
20 and still more preferably within about 10%, of the amount delivered in any
21 other unit of time within the administration period. In some cases, the amount
22 per unit time of LHRH delivered may even remain within about 5%, and even
23 about 3 to 2% within the administration time period.

24
25 Another preferred embodiment of the method utilizes a substantially
26 constant applied electric current. Since in this case, the electric current is
27 applied substantially continuously, the delivery of LHRH through the selected
28 body surface is assumed to occur substantially continuously, i.e., over at least
29 about 80%, preferably at least about 90%, and more preferably at least about
30 95% of the administration period. In some cases, the current may even be
31 applied substantially continuously at least about 98-99%, and even up to

1 100% of the delivery time. Thus, the agent is delivered in a substantially
2 continuous manner and not as a pulse over a short period of time with long
3 periods of time in-between, during which time no delivery is attained. In a
4 most preferred embodiment, LHRH is delivered substantially without
5 interruption during the entire extended delivery period. A preferred rate of
6 delivery of the agent is about 0.01 to 10 mg, and more preferably about 0.05
7 to 5 mg, over a period of about 1 to 10 days, or 500 µg/day to 10 mg/day,
8 preferably 1 mg/day to mg/day and more preferably about 1 mg/day to 5
9 mg/day. The administration of LHRH induces a first initial surge in the serum
10 concentration of luteinizing hormone (LH) and a subsequent increase in
11 follicle stimulating hormone (FSH), progesterone, and estradiol over the
12 following 20 days, all of which are consistent with the induction of ovulation
13 (see, Fig. 2). In another embodiment of the method of this invention, when
14 the electrotransport administration of the LHRH is stopped, a second surge in
15 LH serum concentration is attained, which is indicative of the initiation of an
16 estrous cycle.

17

18 The method of this invention may be custom tailored to obtain any
19 specific birth date, within some margin of error, by calculating back the
20 starting date and period of delivery of LHRH. This may be done taking into
21 consideration the desired birth date, the gestation period of the mammal, and
22 the LHRH delivery period, generally about 1 to 10 days.

23

24 In one preferred embodiment, the present invention is applied to the
25 breeding of horses, by administering LHRH to female equines for the
26 improved breeding of horses, such as thoroughbred race horses. This method
27 is applied to preferably obtain birth dates as close, and subsequent, to
28 January 1 of the following year as possible. Thus, the preferred starting date
29 and period of time for the electrotransport delivery of LHRH to thoroughbred
30 mares are dependent on, and may be calculated, the desired birth date,
31 preferably being as early as January 1, but not before this date, the gestation

1 period of the mare being usually about 335 to 340 days, and the period from
2 initiation of the electrotransport delivery of LHRH to the optimal time for
3 attempting insemination generally being about 5 to 20 days. Considering
4 these factors, the continuous transdermal administration of the LHRH by
5 electrotransport to mares for breeding thoroughbred horses may preferably
6 occur from about, but not before, January 1 to March 30, more preferably
7 from about January 5 to February 15, and most preferably from about
8 January 15 to February 1.

9
10 The transdermal administration of LHRH by electrotransport may also
11 be used to select a desired insemination date. In this embodiment of the
12 invention, LHRH is electrotransported through a body surface of the mammal,
13 e.g., the mare, while it experiences some stage of the estrous cycle. This
14 procedure, restarts the estrous cycle of the mare, and is generally undertaken
15 by substantially continuously delivering LHRH by electrotransport for a period
16 of about 0.5 to 10 days, preferably about 1 to 7 days, and more preferably
17 about 2 to 5 days. Over this period of time, the agent is generally delivered at
18 a rate of about 0.05 to 15 micrograms per hour ($\mu\text{g/hr}$), preferably about 1 to
19 10 $\mu\text{g/hr}$, and more preferably about 5 to 8 $\mu\text{g/hr}$. However, the period and the
20 rate of delivery of LHRH may be varied depending on a number of factors,
21 including the weight of the mammal, e.g., the mare, and its reproductive stage
22 at the time the treatment is started. Regardless of the stage of the estrous
23 cycle, the electrotransport delivery of LHRH to the mammal for the described
24 period of time at the described delivery rate causes the cycle to be started
25 again. Thus, a mammal's cycle may be essentially reset or restarted at any
26 given time by the initiation of electrotransport delivery of LHRH. In this
27 manner, a date may be selected for its insemination by either artificial or
28 natural means, and the initiation time of transdermal electrotransport of LHRH
29 may be calculated based on the knowledge of the time from the initiation of
30 the estrous cycle to the optimal time for insemination, typically about 5 to 20
31 days, and the time from initiation of LHRH electrotransport to the resetting of

1 the estrous cycle, or about 3 to 7 days. For example, assuming that a male
2 mammal, e.g., a stud, will be available on or about June 24, the optimal time
3 to begin the electrotransport delivery of LHRH to the mare would be about
4 June 10 to June 18. However, in some cases, the period may extend beyond
5 these dates.

6

7 Accordingly, the teachings of this invention enable a superior method
8 for controlled breeding of race horses. Generally, this controlled method of
9 breeding entails first delivering LHRH by transdermal electrotransport to a
10 mammal, such as a mare, over a predetermined period of time in a
11 substantially continuous manner, and preferably at a substantially constant
12 rate effective to induce ovulation. A predetermined period of time is then
13 allowed to pass from a date, which is a function of the dates of initiation or
14 cessation of transdermal electrotransport, or both. In one embodiment, this
15 predetermined period may be about 3 to 7 days after initiation of
16 electrotransport delivery. In another embodiment, the period may be within
17 about 2 days of cessation of LHRH electrotransport delivery. During this
18 period subsequent to the cessation of LHRH administration, an endogenous
19 second surge of serum LH concentration generally occurs, which signals the
20 initiation of a newly induced estrous cycle, from which the date of ovulation
21 may be calculated as is known in the art. The mare may be subsequently
22 inseminated, either naturally or artificially, at a time expected to be most likely
23 to achieve impregnation, time which clearly overlaps with the ovulation date,
24 as is known in the art.

25

26 The delivery of LHRH according to the present invention may be
27 accomplished by a number of electrotransport devices. One example of an
28 electrotransport device useful for the practice of the present invention is
29 illustrated in Fig. 1. Device 10 has two current distributing members or
30 electrodes, comprised of electrically conductive materials, referred to herein
31 as a donor electrode 12 and a counter electrode 14. The electrodes may be

1 composed of any materials which are sufficiently electrically conductive
2 including, without limitation thereto, silver, silver chloride, zinc, carbon,
3 platinum, and stainless steel. The electrodes may be provided in a variety of
4 forms including metal foil, screen, coatings or polymer/metal composites. The
5 composites may be formed by numerous processes such as extrusion,
6 calendering, film evaporation, or spray coating. In Fig. 1, the donor and
7 counter electrodes 12 and 14 are positioned adjacent to, and in electrical
8 contact with, the donor reservoir 16 and the counter reservoir 18,
9 respectively. The donor reservoir 16 contains the LHRH to be delivered,
10 preferably in the form of an aqueous solution of a water soluble salt of LHRH.
11 The counter reservoir 18 may contain a biocompatible electrolytic salt such as
12 sodium chloride or another agent to be delivered. The reservoirs are formed
13 of any material adapted to absorb and hold a sufficient quantity of liquid
14 therein in order to permit transport of LHRH/electrolyte therethrough by
15 electrotransport. Preferably, the reservoirs 16 and 18 are formed of one or
16 more hydrophilic polymers such as polyvinylpyrrolidone, polyvinyl alcohol,
17 and/or polyethylene glycols and optionally also contain one or more
18 hydrophobic polymers such as polyisobutylene, polyethylene, or
19 polypropylene. An electrical insulator 20 is positioned between (i) the donor
20 electrode 12 and donor reservoir 16 and (ii) the counter electrode 14 and
21 counter reservoir 18. Insulator 20, which may be an air gap or may be
22 composed of a material which conducts neither electrons nor ions to a
23 substantial extent, prevents device 10 from short-circuiting through a path
24 which does not include the body surface 40 to which the device 10 is applied.
25 The device 10 optionally includes a backing layer 22 composed of a liquid
26 impermeable non-conducting material.

27

28 Device 10 has an electronic circuit, illustrated schematically in Fig. 1 as
29 layer 24, having therein a power source, preferably a DC source, e.g., one or
30 more batteries. Typically, the electronic circuit layer 24 may be comprised of
31 electronically conductive pathways printed, painted or otherwise deposited on

1 a thin, flexible substrate such as, for example, a film or polymeric web, e.g.
2 the electronic circuit layer 24 is a flexible printed circuit. In addition to the
3 power source, the electronic circuit layer 24 may also include one or more
4 electronic components which control the level, wave form shape, polarity,
5 timing, etc., of the electric current applied by device 10. For example, the
6 circuit layer 24 may contain one or more of the following electronic
7 components: control circuitry such as a current controller, e.g. a resistor or a
8 transistor-based current control circuit, an on/off switch, and/or a
9 microprocessor adapted to control the current output of the power source
10 over time. The outputs of the circuit layer 24 are electrically connected to the
11 electrodes 12 and 14 such that each electrode is in electrical contact with an
12 opposite pole of the power source within the circuit layer 24.

13

14 The device adheres to the body surface in this embodiment by means
15 of a peripheral adhesive layer 28. Optionally, the device may contain an in-
16 line adhesive layer, i.e. an adhesive layer positioned between reservoir 16
17 and/or 18 and the body surface of the patient. An in-line adhesive must be
18 composed of an ion-transmitting material, i.e. LHRH must be capable of
19 penetrating the adhesive layer to reach the body surface. Optional flux
20 control membranes 30 and 32 are positioned between the donor reservoir 16
21 and the body surface 40 and between the counter reservoir 18 and the body
22 surface 40, respectively, in order to limit or control the amount of passive, i.e.
23 not electrically assisted, flux of LHRH to the body surface 40.

24

25 The device 10 of Fig. 1 is merely one example of an electrotransport
26 device useful in accordance with present invention. In addition, the system
27 may contain other features, such as a removable protective liner (not shown)
28 on the body surface contacting face 32 of the device. Furthermore, certain
29 components in the device 10 are unnecessary or optional according to the
30 present invention. The counter reservoir 18, the passive flux control
31 membranes 30 and 32, and the peripheral adhesive 28 are all examples of

1 optional components. If the materials of electrodes 12 and 14 form a galvanic
2 couple, the independent power source in layer 24 may also become an
3 optional component. Thus, the device 10 of Figure 1 is presented solely for
4 illustration of one embodiment of the present invention.

5

6 LHRH may be electrotransported through many locations, or body
7 surfaces, on a mammal, such as an equine. For example, an electrotransport
8 device may be affixed to the underside of an animal between the front and
9 hind legs. Alternatively, a device may be located on the interior of a leg,
10 preferably a hind leg because of the larger surface area. Both the interior leg
11 and underside locations are difficult for an animal, such as a horse, to reach.
12 However, the delivery of LHRH from an electrotransport device is preferably
13 accomplished through an area of the neck of the mammal, which is preferred
14 because it is very difficult for the animal to bite, scratch with its legs, or swat
15 with its tail. In addition, the application of an electrotransport device to the
16 neck of a mammal is safer and more convenient for the preparation of the
17 application site, i.e. shaving an area of the horse's neck so that the device
18 may be applied directly to the skin.

19

20 Preferably, when the agent is administered to a mammal, such as a
21 female equine, an area of the underside located between the front and back
22 legs may be utilized, the area is shaven, and an electrotransport device is
23 applied thereto. In other cases, the agent may be administered through an
24 area of the neck of the mammal, which also requires shaving prior to
25 application of the device.

26

27 Prior to applying the device, the selected body surface may be
28 advantageously treated or otherwise prepared to be most suitable for
29 enhancing the delivery rate of the agent. For example, known
30 electrotransport permeation enhancers, such as alcohols, may be utilized in
31 practicing the invention described herein. In the case of delivery of LHRH to

1 an animal such as a mare, the animal's hair is preferably removed from the
2 selected body surface, e.g. by shaving. Hair removal allows the electrodes of
3 the device to be placed in better ion transmitting relation with the skin surface
4 (eg, skin) and also better permits the device to be adhered to the body
5 surface (eg, skin).

6

7 Having thus generally described the invention, and certain preferred
8 embodiments thereof, the invention will be further illustrated with reference to
9 the following example.

10

11 Example 1

12

13 Electrotransport Delivery of LHRH to Anestrous Mares

14

15 A veterinary clinical study was conducted on mares in Ireland (northern
16 hemisphere) during late October. In the study, electrotransport LHRH
17 delivery devices were applied to a group of 3 mares, ages 4 to 7 years.
18 LHRH was delivered to the mares by electrotransport in a continuous manner
19 over a 3 day (72 hour) period.

20

21 The mares were prepped on the inner thigh of the hind leg with #20
22 clipper blade and wiped down with isopropyl alcohol. An active, 2 cm²
23 electrotransport-LHRH patch was applied to each mare on Day 1 of the study.
24 The patches delivered LHRH for 24 hours. New sites were prepped each day
25 of application and a new patch was applied to each mare throughout the
26 three day wearing period. Spent patches, from each 24 hours of wearing,
27 were stripped following application of the new patch. Blood samples were
28 drawn at 24 hours prior to the start of LHRH delivery, and at 0, 0.5, 1.5, 3,
29 4.5, 6, 8, and 24 hours of treatment for each day of application through the
30 three days of LHRH delivery. Twenty-four hour blood samples were then

1 drawn on Days 4, 5, 6, and 7. Blood samples were then drawn at 0, 0.5, 1.5,
2 3, 4.5, and 6 hours of Day 21 of the study to conclude the study.

3

4 Two of the three mares, A and C wore the patches for two sequential
5 24-hour periods. Mare B wore the patch for only one 24-hour period. Figs. 3,
6 4, and 5 show progesterone and LH plasma concentrations of the three
7 mares during the pretreatment, treatment and washout phases.

8

9 The plasma concentrations of progesterone (mg/mL) showed a distinct
10 increase on Day 3 of treatment in mare A and were elevated on Days 4
11 through 7 in mares A and C. In mare B, progesterone concentrations were
12 consistent during the seven days of the feasibility study and on Day 21. The
13 plasma concentrations of luteinizing hormone (mIU/mL) were increased
14 above the normal range throughout the period of treatment (Days 1 through
15 7) in mare B, and on Days 2 through 6 in mares A and C. The increased
16 concentrations of LH were most consistent on Days 4, 5, and 6 (except in
17 mare C). On Day 21, plasma luteinizing hormone concentrations were
18 generally <1.0 mIU/mL. Increased concentrations refer to concentrations
19 >1.5 mIU/mL.

20

21 Mares A and C showed the signs of coming into season. These two
22 mares stood for the teaser stallion on Day 6; whereas, mare B did not show
23 this behavior. These physiological observations are consistent with the blood
24 results obtained in the study for mares A and C which wore the patches for
25 two sequential 24 hour periods.

26

Example 2**Electrotransport Delivery of LHRH to Mares**

A veterinary clinical study was conducted on twelve mares in Ireland over a twenty-one day period beginning on April 21st. Since mares in Ireland would naturally be coming out of anestrus during this time frame, the results of this study may not be probative of the effectiveness of transdermal electrotransport LHRH delivery for starting the estrous cycles of anestrus mares. Nevertheless, the study does show the effectiveness of the devices and clinical methods used in the study for transdermally delivering LHRH into the blood of breeding mares.

Thirty electrotransport delivery devices were produced having the construction illustrated, in exploded view, in Fig. 6, fifteen of the devices having a 1 cm² area and 15 having a 2 cm² area. The current density used was 0.1 mA/cm², and the total current for the 1 cm² device was a 0.1 mA while the total current for the 2 cm² device was 0.2 mA.

Double sided adhesive foam tape having a thickness of 0.8 mm (1/32 in.) was folded over on itself to create a foam layer 302 having a thickness of 1.6 mm (1/16 in.). Then, by use of a NAFE punch press, openings 304, 306 were punched out with the die. Gel reservoirs 308, 310 having the same composition as the cathodic hydrogels described in Example 1 were inserted into the openings 304, 306.

A silver foil anodic electrode 312 was placed over the gel 310 and a silver chloride-loaded ethylene vinyl acetate film electrode 314 was placed over gel 308. The electrodes 312, 314 were electrically connected to the outputs 315a, 315b of a printed circuit board assembly 316 by means of

1 electrically conductive adhesive strips 318a, 318b (Arclad 8001, Adhesives
2 Research, Allentown, PA), respectively. The top of the circuit board assembly
3 316 was Medpar pigmented film 320 (3M Company, St. Paul, MN). The skin
4 side of gel 310 was covered with an anion exchange membrane 322 (Sybron
5 MA 3475, The Electrosynthesis Co., E. Amherst, NY) which is impermeable to
6 cations. A layer 324 of single sided adhesive foam had an opening 326
7 punched out using the punch press. A LHRH-containing gel reservoir 328
8 having the same composition as the anodic hydrogel described in Example 1
9 was inserted into the opening 326. The openings 310 and 326 had the
10 same cross-sectional size and shape so they were aligned on top of one
11 another, with the anion exchange membrane 322 sandwiched therebetween.
12 A 0.03 mm (1 mil) thick silicone coated polyester release liner 330 was placed
13 over the skin-contacting surfaces of the device until use.

14

15 The circuit board assembly applied electrotransport currents of 0.1 mA
16 or 0.2 mA, depending upon the cross-sectional areas of gels 308, 310 and
17 328. For those devices having gels with a cross-sectional area of 2 cm², the
18 applied current was 0.2 mA. For those devices having gels with a cross-
19 sectional area of 1 cm², the applied current was 0.1 mA. Thus, the applied
20 current density was 0.1 mA/cm² for all systems.

21

22 A blood sample was taken from each mare 24 hours prior to
23 application of the device to establish a pretreatment baseline. During the 5
24 day application period, blood samples were taken daily at 2 hrs, 6 hrs, and 24
25 hrs, from the time of initial application of the device.

26

27 Subsequent to the removal of the device, blood samples were
28 collected once daily for 15 days until day 20 from the date of the initial
29 application of the device. Lithium heparin was added to the blood samples

1 which were centrifuged to separate out the blood plasma fractions which were
2 stored at -20°C until assayed.

3

4 All plasma samples were analyzed for progesterone, LH, FSH and
5 estradiol. Progesterone was determined by an ELISA (Enzyme Linked
6 Immuno-Sorbent Assay), and the levels of luteinizing hormone (LH), follicle-
7 stimulating hormone (FSH), and estradiol were determined by
8 radioimmunoassays.

9

10 When the devices were applied to the mares, a corresponding rise in
11 LH was observed after 2 hrs., and the level of LH in serum remained higher
12 than the baseline even after 24 hrs. The LHRH was, thus, absorbed quickly
13 through the skin.

14

15 Table 1 below shows the serum levels of LH for each mare from day -1
16 to day 20 of the study period.

17

18

1 Table 1: Luteinizing Hormone (LH) Serum Levels (mIU/ml)

2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28	Mare Number											
	Day	1	2	3	4	5	7	8	9	10	11	12
-1		<1	<1	2.2	4.6	4.6	3.4	1.7	5.4	3.8	2.2	5.0
1		4.1	7.0	6.5	7.5	6.1	10.5	5.3	8.1	6.6	6.9	7.4
2		3.8	6.2	5.5	6.6	5.5	4.5	5.7	7.4	6.2	6.9	8.7
3		7.7	4.6	3.4	5.8	4.1	4.3	5.1	5.2	4.2	4.8	9.3
4		2.4	3.6	3.1	3.7	2.6	3.7	3.5	4.9	2.4	3.7	4.9
5		2.9	3.5	3.1	4.5	3.5	3.7	3.8	4.8	3.0	4.6	3.9
6		2.5	2.5	3.4	4.2	3.4	2.8	1.0	3.0	3.8	4.6	7.7
7		4.8	3.0	6.2	5.0	6.8	7.5	4.4	7.5	7.5	6.2	7.5
8		6.2	4.0	5.4	7.5	6.8	8.5	6.8	7.0	7.5	8.5	7.5
9		6.8	6.8	7.0	8.0	6.2	9.0	6.8	7.5	7.0	7.5	5.4
10		5.4	6.0	3.6	8.0	6.8	5.4	4.4	7.0	5.0	5.0	7.5
11		5.4	5.4	5.4	6.8	4.8	6.8	4.0	7.0	6.2	8.0	8.5
12		6.2	7.5	5.0	8.0	6.8	6.2	5.4	8.0	7.0	7.5	8.5
13		8.5	7.0	6.8	7.0	6.2	6.8	6.2	8.0	6.0	7.5	7.5
14		6.2	6.2	5.0	8.5	6.0	7.5	4.4	7.5	6.8	7.5	7.5
15		6.2	6.0	7.0	8.0	3.4	7.0	3.8	6.0	4.4	4.6	6.0
16		2.2	4.6	3.4	5.4	1.7	3.4	3.8	4.2	5.0	5.4	4.4
17		3.8	4.2	5.0	7.5	4.2	4.2	4.2	7.5	4.4	4.4	7.0
18		3.4	4.2	1.4	5.4	1.7	4.4	23.0	6.0	4.4	6.0	4.4
19		2.5	2.2	2.5	6.0	2.9	5.4	2.9	4.4	4.6	8.0	7.5
20		3.4	2.2	3.4	7.0	2.9	4.2	2.2	4.2	8.5	3.4	6.0

29 The serum concentrations of FSH (mIU/ml), progesterone (ng/ml), and
 30 estradiol (pg/ml) were also obtained for mares 1 to 5 and 7 to 12 as a function
 31 of the day relative to the initiation of the electrotransport treatment.
 32

33
 34 Mares 1 to 5 and 7 to 12 were rectally examined by a veterinary
 35 surgeon to determine the stage of their estrous cycle. The rectal
 36 examinations were performed prior to the electrotransport LHRH treatment

described above and on days 3, 5, 8, 10, 13, 15, 17 and 20. Table 3 below shows the observations made 1 day prior to starting treatment.

Table 2: Veterinary's Observations One day prior to Treatment

Mare	Left Ovary	Right Ovary	Cervix Size
1	+	2 B-C	3 Fingers
2	+	-	2 Fingers
3	-	2 B-C	2 Fingers
4	About Ovulate	Small Inactive	Closed
5	-	2 1/2 B	5 Fingers
7	++	2	4 Fingers
8	Ovulated	Ovulated	Closed
9	Inactive	-	2 Fingers
10	Ovulated	2 1/2	1 Finger
11	2 1/2 B	-	5 Fingers
			Wide Open
12	2 1/2	Ovulated	Closed

1 Table 3 below shows the observations made on day 15 after starting
2 treatment.

3

4 Table 3: Veterinary's Observations Made on day 15 after Starting Treatment

5

6

7	Mares	Left Ovary	Right Ovary	Cervix
8				
9				
10	1	L+	2 1/2 B-C	2 Fingers
11	2	L-	R2	Open
12	3	L+	R+	Closed
13	4	L+	R-	Closed
14	5	L2C	R3B	Open
15	7	Ovulated	-	Closed
16	8	L2	R2	Closed
17	9	Inactive	R-	2 Fingers
18	10	LP 3 1/2b	R2C	2 Fingers
19	11	L3B	-	Open
20	12	L2	R-	Closed
21				

22

23

24 From the data shown in Table 2, it appears that most, if not all, of the
25 twelve mares were in mid-estrous cycle prior to starting the LHRH treatment
26 regimen. By the fifth day of LHRH treatment, the majority of the animals had
27 come into heat and had stood for the teaser. This can be deduced from the
28 size of the animal's cervix, given that as an animal comes into estrous, its
29 cervix dilates. At the end of the trial, all animals had come into estrous.

30

1 The blood concentrations of LH on day -1, the day prior to starting
2 treatment, varied from about 0 to 5 mIU/ml, since the mares were at various
3 stages of their estrous cycles. However, upon receiving the present
4 treatment, i.e., after the initiation of LHRH electrotransport, all mares appear
5 to have experienced the same general trend in LH concentrations in blood. A
6 surge in LH concentration was experienced by all mares from about day 0
7 through day 2, which was elicited by the administration of the LHRH. Then, a
8 decrease in LH concentration in blood occurred, with a minimum reached on
9 day 5, the final day of administration of LHRH by electrotransport. After
10 removal of the electrotransport device, the LH concentration in blood
11 increased beginning on day 5, and reached a plateau on days 7 to 10. A drop
12 in the LH serum concentration was finally observed beginning around days 14
13 to 15.

14

15 Having thus generally described the invention, and described in detail
16 certain preferred embodiments thereof, it will be readily apparent that various
17 modifications to the invention may be made by those skilled in the art, without
18 departing from the scope of this invention, which is limited only by the
19 following claims.

20

1 CLAIMS:

2

3 1. A method of inducing ovulation in a female mammal having
4 seasonal estrous and anestrus periods, comprising administering an agent
5 selected from the group consisting of LHRH, prodrugs of LHRH, analogs of
6 LHRH, salts thereof and mixtures thereof, to the mammal during a seasonal
7 anestrus period through a body surface of the mammal over a period of
8 time effective to induce ovulation in the mammal.

9

10 2. The method of claim 1, including inseminating the mammal after
11 inducing ovulation.

12

13 3. The method of claim 1, wherein the agent is continuously
14 delivered by electrotransport for at least about 80% of the administration
15 period.

16

17 4. The method of claim 3, wherein the predetermined time is about
18 3 to 7 days after initiating the electrotransport administration of the agent.

19

20 5. A method of inducing ovulation in a female mammal having
21 seasonal estrous and anestrus periods, comprising administering an agent
22 selected from the group consisting of LHRH, prodrugs of LHRH, analogs of
23 LHRH, salts thereof and mixtures thereof, to the mammal during a seasonal
24 estrus period by electrotransport through a body surface of the mammal
25 over a period of time effective to restart the estrus cycle of the mammal.

26

27 6. The method of claim 5, including inseminating the mammal after
28 inducing ovulation.

29

30

1 7. The method of claim 1, wherein the agent is delivered at a rate
2 of about 0.1 to 10 mg over a period of about 1 to 10 days.

3

4 8. The method of claim 7, wherein the agent is delivered at a rate
5 of about 0.5 to 5 mg.

6

7 9. The method of claim 1, wherein the agent is continuously
8 delivered at a rate of about 0.05 to 15 $\mu\text{g/hr}$.

9

10 10. The method of claim 9, wherein the agent is continuously
11 delivered at a rate of about 0.5 to 10 $\mu\text{g/hr}$.

12

13 11. The method of claim 1, wherein the body surface comprises skin
14 of the mammal.

15

16 12. The method of claim 11, including shaving the skin of the
17 mammal before administering the LHRH.

18

19 13. The method of claim 11, wherein the skin is a skin site selected
20 from the group consisting of an area of the underside of the mammal, the
21 underside of the mammal between the front legs, an interior surface of a leg,
22 and the neck of the mammal.

23

24 14. The method of claim 1, wherein the agent is administered to a
25 mammal located in the northern hemisphere between about January 1 and
26 March 1.

27

28 15. The method of claim 1, wherein the LHRH is delivered at a
29 substantially constant rate during the period of time.

30

1 16. The method of claim 1, including delivering a permeation
2 enhancer to the body surface.

3

4 17. The method of claim 1, wherein the female mammal is a mare.

5

6 18. The method of claim 5, wherein the female mammal is a mare,
7 and the administration of the agent is initiated between about January 1 and
8 March 1.

9

10 19. The method of claim 1, wherein the mammal is a mare and the
11 insemination is with sperm from a thoroughbred horse.

12

13

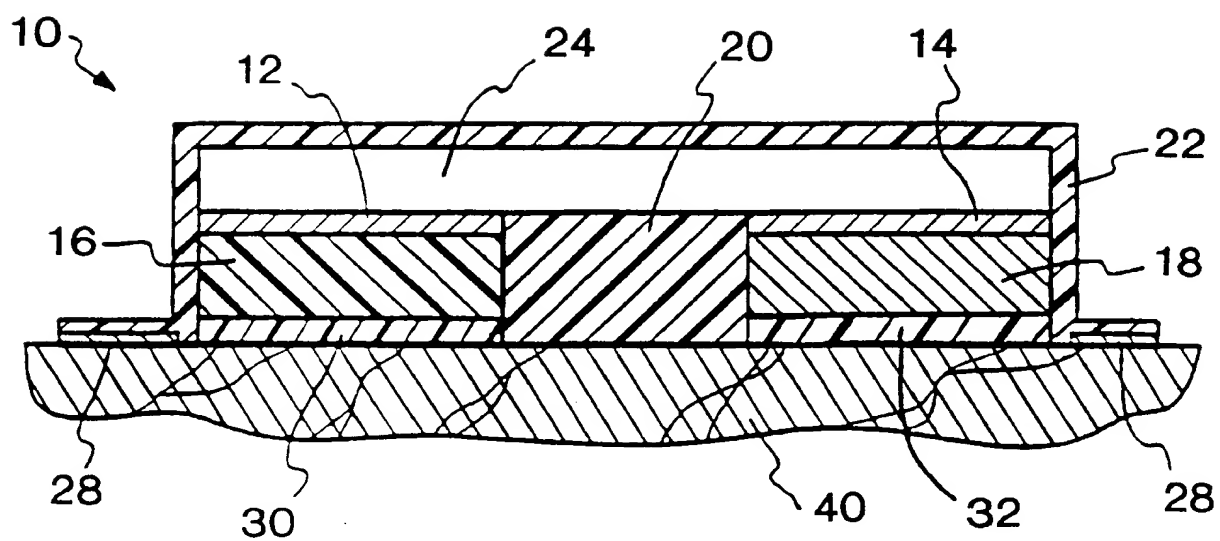


FIG.1

2 / 6

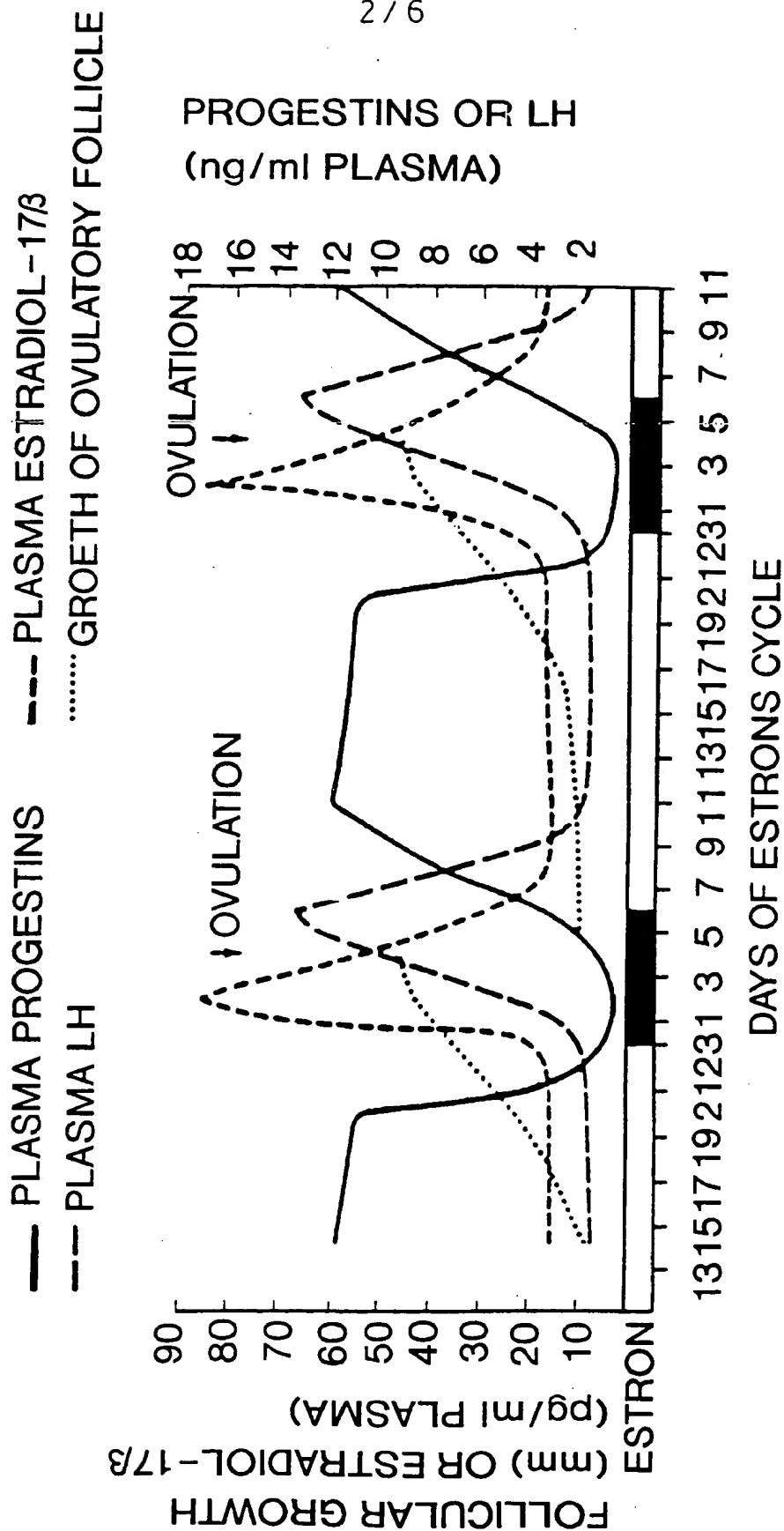


FIG.2

3 / 6

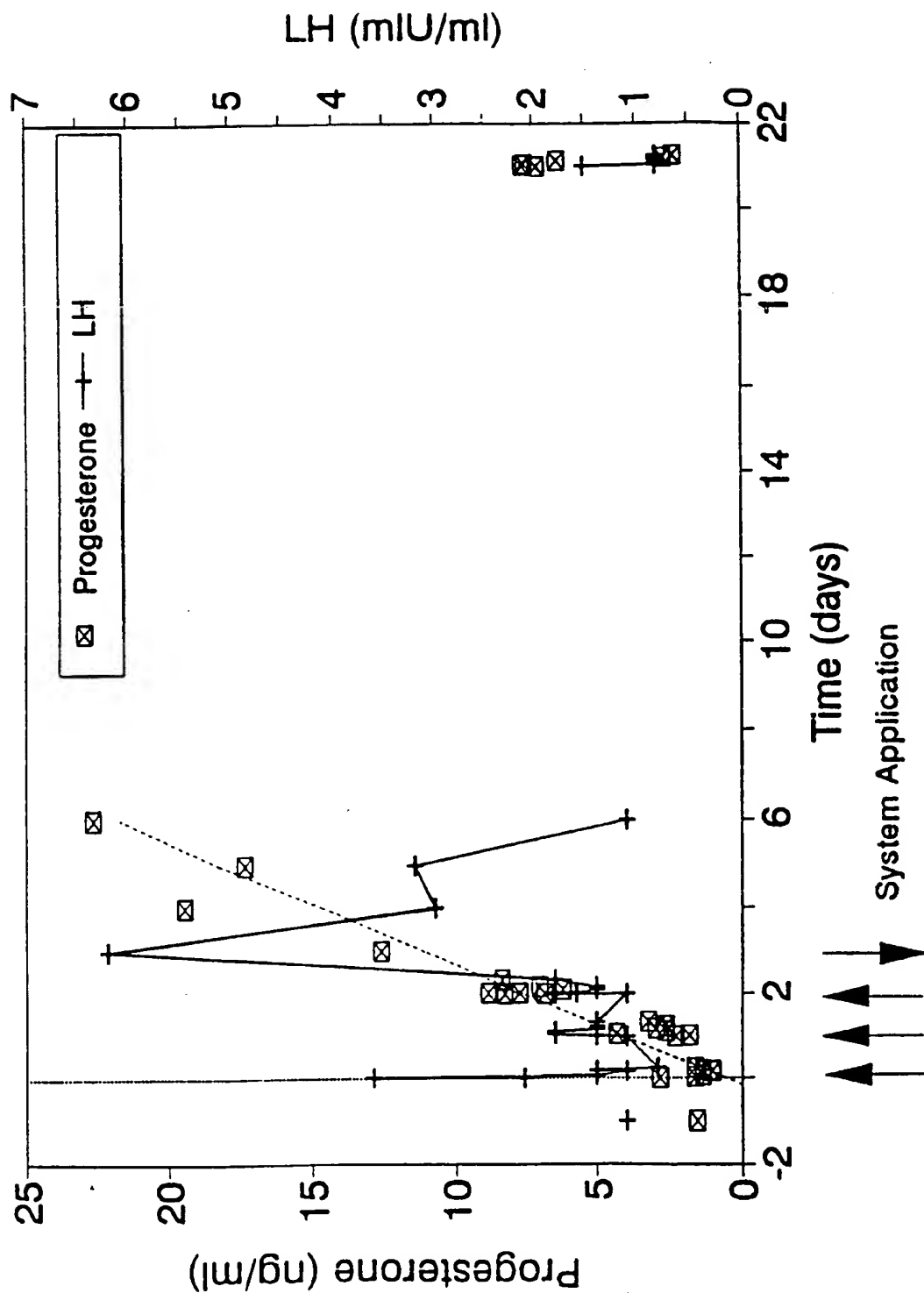
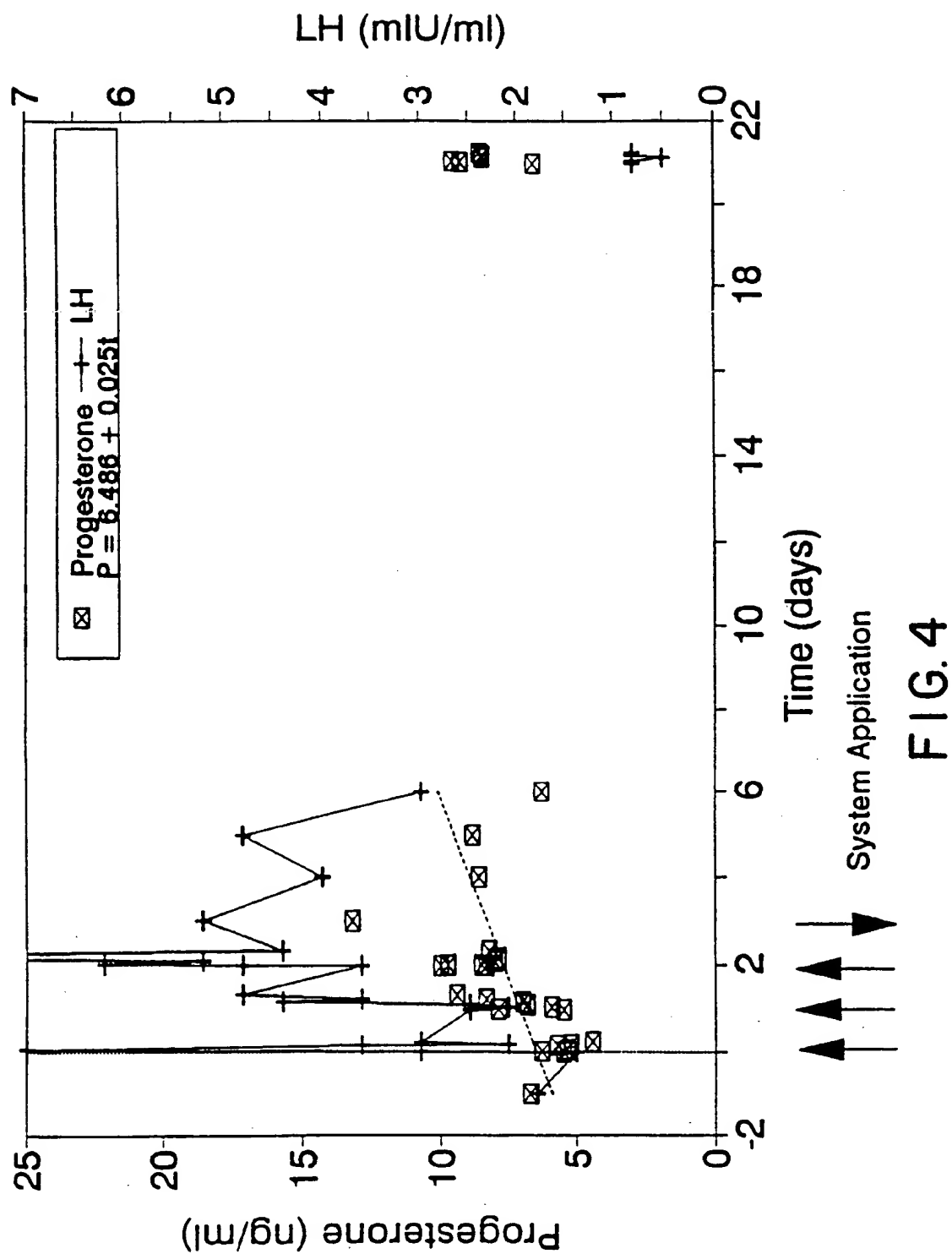


FIG. 3

4 / 6



5/6

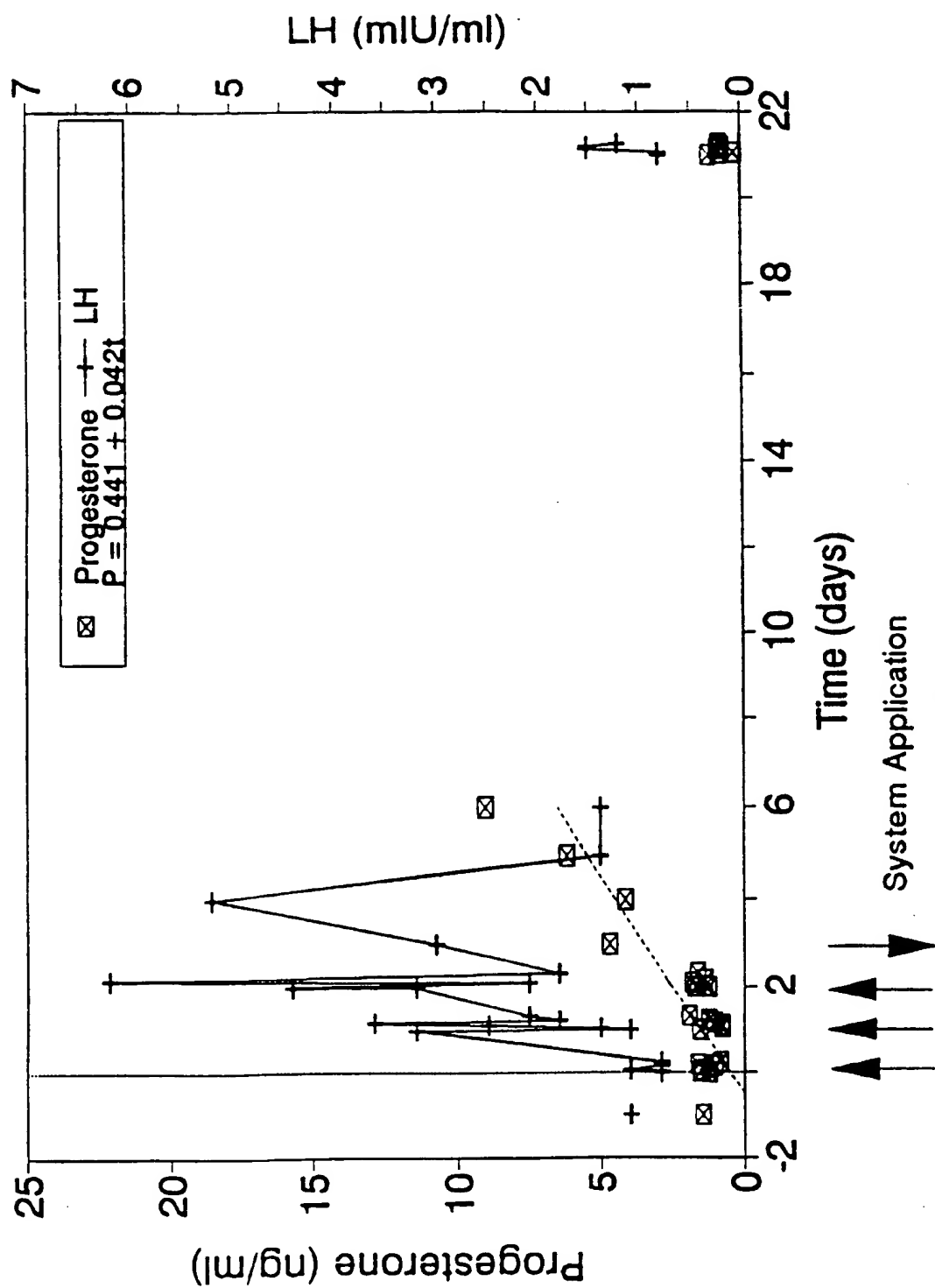


FIG. 5

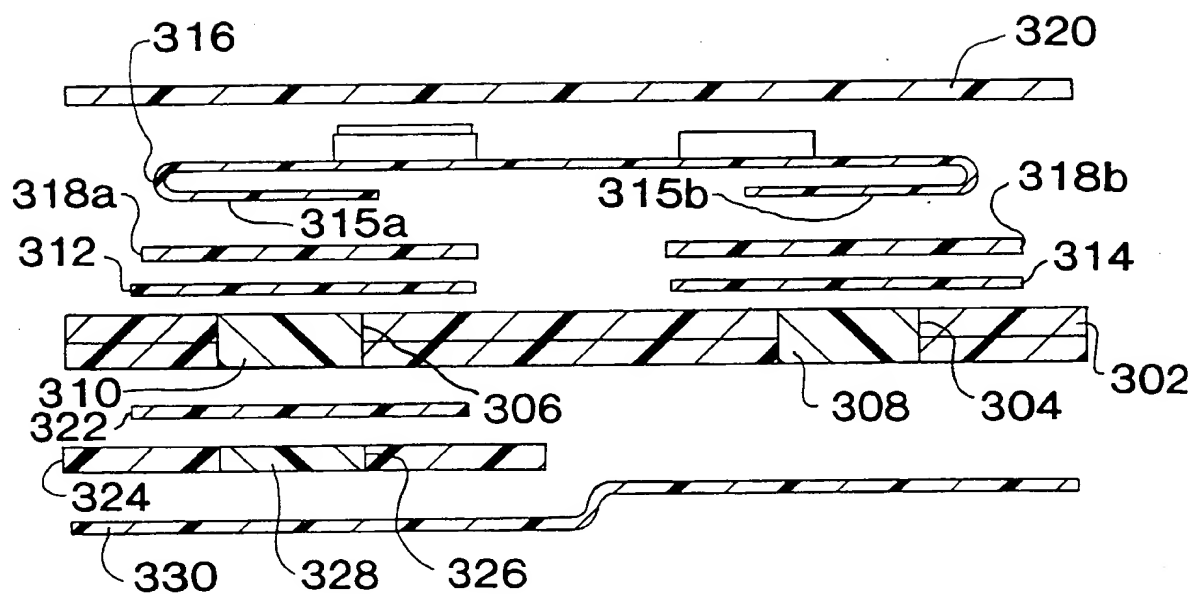


FIG. 6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23345

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/30 A61N1/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y A	J.E.TURNER,C.H.G.IRVINE: "The effect of various gonadotrophin-releasing hormone regimens on gonadotrophins,follicular growth and ovulation in deeply anoestrous mares" JOURNALS OF REPRODUCTION & FERTILITY LTD, vol. 44, 1991, GREAT BRITAIN, pages 213-213-225, XP002064443 cited in the application see page 213, line 1 - line 15 see page 222, line 17 - page 224, line 24; figures --- -/--	1,2,5-8, 11,17 4,7-10, 15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

8 May 1998

Date of mailing of the international search report

22/05/1998

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/23345

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 372 579 A (SIBALIS DAN) 13 December 1994 cited in the application see column 5, line 51 - column 8, line 26; figures ---	1,4,5,7, 8,11,15, 16
A	WO 93 03790 A (UNIV RUTGERS) 4 March 1993 see abstract; figures -----	1,3,5,11

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Form PCT/ISA/210 (patent family annex) (July 1992)